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(54) **PREPARATIONS SOLIDES DE PRINCIPES ACTIFS, CONTENANT DE L'HYDROXYPROPYLCELLULOSE**

(54) **SOLID ACTIVE INGREDIENT COMPOSITIONS CONTAINING HYDROXYPROPYLCELLULOSE**

(57) La présente invention concerne des préparations contenant des principes actifs, que l'on obtient par extrusion d'un mélange en fusion comprenant A) une hydroxypropylcellulose thermoplastique, soluble dans l'eau, B) un ou plusieurs principes actifs, C) si on le désire, des produits auxiliaires pharmaceutiques, la proportion de A) représentant de 10 à 30 % en poids par rapport à l'ensemble de la préparation.

(57) Preparations containing active agents obtainable by the melt extrusion of A) a water-soluble thermoplastic hydroxypropyl cellulose, B) one or more active agents, C) if desired, pharmaceutical auxiliaries, in which the proportion of A) is 10 to 30 % wt. in relation to the entire preparation.

Solid active ingredient compositions containing hydroxypropylcellulose

The present invention relates to solid active ingredient-containing compositions obtainable by melt extrusion of a mixture of

A) a water-soluble thermoplastic hydroxypropylcellulose,

B) one or more active ingredients and

C) if required conventional pharmaceutical ancillary substances,

where the content of A) is from 10 to 30% of the total weight of the mixture.

The invention furthermore relates to a process for producing compositions of this type and to drug forms from these compositions. Melt extrusion and its use in pharmaceutical technology is generally known.

US-A 4 801 460 describes the production of solid drug forms by melt extrusion of mixtures of active ingredient and thermoplastic N-vinylpyrrolidone polymers.

JP-A 58-79915 and JP-A 58-192817 disclose the production of rod-shaped drug forms by melt extrusion of water-soluble polymers such as hydroxypropylcellulose (HPC) or mixtures of HPC with other polymers.

EP-A 596 203 describes active ingredient-containing compositions which are obtained by mixing the active ingredient with a water-soluble melt of two polymers which differ in viscosity, for example polymer mixtures of hydroxypropylcellulose and hydroxypropylmethylcellulose.

Active ingredient compositions disclosed to date usually have relatively high polymer contents. Although high polymer contents result in good processability, the lower active ingredient contents which inevitably result therefrom, that is to say a low dose of active ingredient with a high tablet weight, may make the entire production process uneconomic.

If, for example, the active ingredient content in a tablet is originally 40% by weight, for the same dosage the tablet weight could be halved when the active ingredient content is doubled.

Thus, for a given extruder melt output, the production capacity of the extruder could be doubled.

On the other hand, in the case of active ingredients requiring a low dose, a high active ingredient content would lead to drug forms whose total weight would be so low that it would be difficult to handle such a small drug form. However, in such cases, it would be just as worthwhile to limit the content of the relatively high-cost polymers. In order for the weight of the drug forms not to be less than the reasonable minimum, it would be worthwhile to replace part of the more costly polymer component by low-cost, not necessarily meltable ancillary substances.

It is an object of the present invention to find compositions which have a low polymer content while permitting melt processing of the composition so that the content of active ingredient or active ingredient and low-cost ancillary substances in the composition can be at a maximum.

We have found that this object is achieved by the compositions defined at the outset, and by a process for producing them, and the use thereof.

The component A) used according to the invention is a water-soluble thermoplastic hydroxypropylcellulose which preferably has a molar degree of substitution of from 3.0 to 4.4. "Molar degree of substitution" refers to the average number of moles of propylene oxide which have reacted per glucose unit in the cellulose.

The hydroxypropylcellulose can have melt viscosities measured by the DIN 53735 method in the range from 0.075 to 54.8 g/10 min.

The molecular weight of the hydroxypropylcellulose can vary within wide limits depending on whether slower or faster release of active ingredient is desired. Hydroxypropylcellulose with molecular weights in the range from 200,000 to 1,500,000 is suitable in particular for producing drug forms in which slow release of active ingredients is desired, since the polymers of higher molecular weight dissolve less well, and only with swelling, in water.

If, however, it is intended to produce drug forms with faster release of active ingredient, it is advisable to use polymers of lower molecular weight which are readily soluble in water, it being possible in this case to use hydroxypropylcellulose with a molecular weight of from 60,000 to 200,000, preferably 60,000 to 100,000.

The preparation of the hydroxypropylcellulose used according to the invention is generally known.

The content of hydroxypropylcellulose in the composition is from 10 to 30%, preferably 20 to 30%, of the total weight thereof.

Suitable as component B) in the compositions are active ingredients or mixtures of active ingredients which are thermally stable under the processing conditions.

Examples of suitable active ingredients according to the invention are:

acebutolol, acetylcysteine, acetylsalicylic acid, aciclovir, alprazolam, albumin, alfacalcidol, allantoin, allopurinol, ambroxol, amikacin, amiloride, aminoacetic acid, amiodarone, amitriptyline, amlodipine, amoxicillin, ampicillin, ascorbic acid, aspartame, astemizole, atenolol, beclometasone, benserazide, benzalkonium hydroxide, benzocaine, benzoic acid, betametasone, bezafibrate, biotin, biperiden, bisoprolol, bromazepan, bromhexine, bromocriptine, budesonide, bufexamac, buflomedil, buspirone, caffeine, camphor, captopril, carbamazepine, carbidopa, carboplatin, β-carotene and other carotenoids, cefachlor, cefalexin, cefadroxil, cefazolin, cefixime, cefotaxime, ceftazidine, ceftriaxone, cefuroxime axetil, chloramphenicol, chlorhexidine, chlorpheniramine, chlortalidone, choline, ciclosporin, cilastatin, cimetidine, ciprofloxacin, cisapride, cisplatin, clarithromycin, clavulanic acid, clomipramine, clonazepam, clonidine, clotrimazole, clozapine, codeine, colestyramine, cromoglicic acid, cyanocobalamin, cyproterone desogestrel, dexamethasone, dexpanthenol dextromethorphan, dextropropoxiphene, diazepam, diclofenac, digoxin, dihydrocodeine, dihydroergotamine, diltiazem, diphenhydramine, dipyridamole, dipyrone, disopyramide, domperidone, dopamine, enalapril, ephedrine, epinephrine, ergocalciferol, ergotamine, erythromycin, estradiol, ethinylestradiol, etoposide, Eucalyptus globulus, fam-otidine, felodipine, fenofibrate, fenoterol, fentanyl, flavin mononucleotide, fluconazole, flunarizine, fluorouracil, fluoxetine, flurbiprofen, furosemide, gemfibrozil, gentamicin, Ginkgo biloba, glibenclamide, glipizide, Glycyrrhiza glabra, guaifenesin, haloperidol, heparin, hyaluronic acid, hydrochlorothiazide, hydrocodone, hydrocortisone, hydromorphon, ipratropium hydroxide, ibuprofen, imipenem, indomethacin, iohexol, iopamidol, isosorbide dinitrate, isosorbide mononitrate, isotretinoin, ketotifen, ketoconazole, ketoprofen, ketorolac, labetalol, lactulose, lecithin, levocarnitine, levodopa, levoglutamide, levonorgestrel, levothyroxine, lidocaine, lipase, lisinopril, loperamide, lorazepam, lovastatin, medroxyprogesterone, menthol, methotrexate, me-

thyldopa, methylprednisolone, metoclopramide, metoprolol, miconazole, midazolam, minocycline, minoxidil, misoprostol, morphine, multivitamins and minerals, nystatin, N-methyl-ephedrine, naftidrofuril, naproxen, neomycin, nicardipine, nicergoline, nicotinamide, nicotine, nicotinic acid, nifedipine, nimodipine, nitrendipine, nizatidine, norethisterone, norfloxacin, norgestrel, nortriptlyine, ofloxacin, omeprazole, ondansetron, pancreatin, panthenol, pantothenic acid, paracetamol, penicillin G, penicillin V, phenobarbital, pentoxifylline, phenylephrine, phenylpropanolamine, phenytoin, piroxicam, polymyxin B, povidone-iodine, pravastatin, prazosin, prednisolone, propafenone, propranolol, pseudoephedrine, pyridoxine, quinidine, ramipril, ranitidine, reserpine, retinol, riboflavin, rifampicin, rutoside, saccharin, salbutamol, salcatonin, salicylic acid, selegiline, simvastatin, somatotropin, sotalol, spironolactone, sucralfate, sulbactam, sulfamethoxazole, sulpiride, tamoxifen, tegafur, teprenone, terazosin, terbutaline, terfenadine, theophylline, thiamine, ticlopidine, timolol, tranexamic acid, tretinoin, triamcinolone acetonide, triamterene, trimethoprim, troxerutin, uracil, valproic acid, vancomycin, verapamil, vitamin E, folinic acid, zidovudine.

Crop protection agents are also suitable as active ingredients.

The amount of active ingredient component B) in the complete composition may vary within wide limits depending on the activity. Thus, the content of B) can be from 0.1 to 90% of the total weight of the composition.

The compositions according to the invention can furthermore contain as components C) conventional pharmaceutical ancillary substances as long as they are thermally stable under the processing conditions, eg. fillers or extenders, lubricants, plasticizers, stabilizers, dyes or pigments, disintegrants, preservatives or flavorings. Examples of suitable fillers are organic compounds such as lactose or mannitol or inorganic substances such as silica or silicates, oxides of magnesium, aluminium or titanium. Fillers which are readily soluble in water, such as lactose or mannitol, are suitable, for example, for producing compositions with an increased rate of release of active ingredient.

The content of fillers in the composition depends on the dosage of active ingredient. In the case of active ingredients with low dosage, it is possible according to the invention to achieve, by higher filler contents, a higher tablet weight without adversely affecting the melt processability. In the case of active ingredi-

ents requiring very low doses, the amount of filler can be up to about 90% by weight.

Further pharmaceutical ancillary substances which can be used are flow regulators such as mono-, di- and triglycerides of long-chain fatty acids such as C_{12}-, C_{14}-, C_{16}- and C_{18} fatty acids or waxes such as carnauba wax, in the conventional amounts.

Examples of plasticizers which may be mentioned are besides low molecular weight polyalkylene oxides such as polyethylene glycol, polypropylene glycol and polyethylene/propylene glycol, also polyhydric alcohols such as propylene glycol, glycerol, pentaerythritol and sorbitol, and sodium diethyl sulfosuccinate, glycerol mono-, di- and triacetate, and polyethylene glycol stearate. In these cases, the amount of plasticizer is about 0.5 to 15, preferably 0.5 to 5, % by weight.

Examples of lubricants which may be mentioned are stearates of aluminum or calcium, and talc and silicones, the amount thereof being about 0.1 to 5, preferably 0.1 to 3, % by weight.

Examples of stabilizers which may be mentioned are light stabilizers, antioxidants, radical traps and stabilizers against microbial attack, all of which can be used in conventional amounts.

In order to produce the compositions according to the invention, the active ingredient component can be either melted directly in the form of a physical mixture with the polymer A) or mixed with the polymer melt which has already been produced.

Otherwise, the component is mixed with the melt in a conventional way in extruders, preferably in single or twin screw extruders at a temperature in the range from 50 to 200°C. The active ingredient-containing polymer melt can be shaped to the compositions according to the invention for example by calendering the extrudate by the method described in EP-A 240 906, and by the processing method disclosed in DE-A 38 30 335 by comminuting the extrudate with rotating knives into places of equal volume which are still shapable. The cooled melt can also be processed to granules.

It is possible to mix the ancillary substances into the melt of active ingredients and polymer A). It is furthermore possible to incorporate the ancillary substances together with the active ingredient into the polymer melt. It is additionally possible to melt mixtures of ancillary substances, the active ingredient and

the polymer A) directly. It is generally customary to melt a physical mixture of ancillary substances, active ingredients and polymers together.

The compositions according to the invention are used as drugs in the form of tablets or granules or employed as pellets in capsules.

If required, the solid pharmaceutical form can also be provided with a conventional coating to improve the appearance and/or taste (coated tablet) or to reduce the rate of release of active ingredient.

The present invention makes it possible to produce in a simple manner solid active ingredient compositions by melt extrusion, it being possible owing to the use of a specific polymer component to keep the polymer content low without adversely affecting the melt processability of the composition. It is possible in this way for a large part of the formulation to consist of active ingredient and low-cost ancillary substances. This makes it possible for solid drug forms to be produced at particularly reasonable cost. Particularly in the case of active ingredients requiring low doses it is possible according to the invention to produce drugs of sizes which are easily handled by melt extrusion of the compositions without the need to use a larger content of the comparatively high-cost polymer.

Example 1

8.0 kg of ambasilide (INN) are extruded with 2.0 kg of a hydroxypropylcellulose with a degree of substitution of 3.0-4.4 and a DIN 53735 melt viscosity of 0.076 g/10 min in a twin screw extruder (ZSK-40 from Werner + Pfleiderer, Stuttgart) under the following conditions:

Shot 1:	90°C
Shot 2:	120°C
Shot 3:	110°C
Shot 4:	110°C
Head:	120°C
Dies:	120°C

The throughput was 20 kg/h (weigh feeders). The hard homogeneous melt was directly compressed to tablets weighing 500 mg in a molding calender located in front of the extruder head.

Example 2

The release of the active ingredient from the tablets from the example was investigated by the USP XXI paddle method under the following conditions:

- stirrer speed 75 rpm
- release medium simulated gastric fluid (USP) pH 1.0
- temperature 37°C
- determination of active ingredient content in the release medium by UV spectroscopy

Measured active ingredient release:

Time [min]	Active ingredient release (in [%])
0	0
15	9.0
30	13.6
45	17.5
60	21.1
270	60.0

We claim:

1. An active ingredient-containing composition obtainable by melt extrusion of a mixture of

   A) a water-soluble thermoplastic hydroxypropylcellulose,

   B) one or more active ingredients and

   C) if required conventional pharmaceutical ancillary substances,

   where the content of A) is from 10 to 30% of the total weight of the mixture.

2. A composition as claimed in claim 1, containing hydroxypropylcellulose with a molar degree of substitution of from 3.0 to 4.4

3. A process for producing an active ingredient-containing composition as claimed in claim 1 or 2, which comprises processing a mixture of

   A) a water-soluble thermoplastic hydroxypropylcellulose,

   B) one or more active ingredients and

   C) if required conventional pharmaceutical ancillary substances,

   where the content of A) is from 10 to 30% of the total weight of the mixture, to a melt and further processing with shaping of particles.

4. The use of the compositions as claimed in claim 1 or 2 for the production of drugs.

5. A solid drug form from the compositions as claimed in claim 1 or 2.

6. The use of the compositions as claimed in claim 1 or 2 for food supplementation.